

THE ANALGESIC EFFECT OF
A NEW IBUPROFEN FORMULATION
ON ODONTOGENIC PAIN

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ABSTRACT

Tanjit S. Taggar: The Analgesic Effect of a new Ibuprofen Formulation on Odontogenic Pain
(Under the direction of Asma Khan)

Ibuprofen sodium dihydrate, a new formulation of ibuprofen, has been introduced with the claim of faster onset of analgesia. To our knowledge, the onset and efficacy of ibuprofen sodium dihydrate in patients experiencing endodontic pain is yet to be evaluated. We conducted a randomized, double blind controlled clinical trial comparing conventional ibuprofen acid and ibuprofen sodium dihydrate (N=41). Written informed consent was obtained from patients experiencing moderate to severe pain and diagnosed with symptomatic irreversible pulpitis and symptomatic apical periodontitis. Baseline measurements included pain intensity and mechanical pain thresholds. Patients were then given 400mg of ibuprofen acid or an equivalent dose of 512mg of ibuprofen sodium dihydrate and instructed to stop a stopwatch when they experience 50% pain relief. At 60 minutes after administration of the analgesic, measurements of pain intensity and mechanical pain thresholds were collected. There was a 50.8% decrease of pain intensity after the use of ibuprofen sodium dihydrate ($P<0.001$) and a 33.3% decrease of pain intensity after the use of ibuprofen acid ($P<0.001$). There was a 15% difference in the change of mechanical allodynia ($P<0.05$) in the ibuprofen sodium dihydrate group and a 9% difference in the change of mechanical allodynia in the ibuprofen acid group ($P>0.05$). The median time to onset of 50% pain relief in the ibuprofen sodium dihydrate group was 26.5 minutes as compared to 44.0 minutes in the ibuprofen acid group ($P=0.08$).

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TABLE OF CONTENTS

LIST OF TABLES.....	vii
LIST OF FIGURES.....	viii
REVIEW OF LITERATURE.....	1
Section 1.1: Introduction.....	1
Section 1.2: Pain perception.....	5
Section 1.3: Acute Inflammation.....	7
Section 1.4: Symptomatic Irreversible Pulpitis.....	9
Section 1.5: Symptomatic Apical Periodontitis.....	11
Section 1.6: Mechanical Allodynia.....	13
Section 1.7: Measuring Pain in Patients.....	14
Section 1.8: Measuring Mechanical Allodynia.....	14
Section 1.9: Visual Analog Scale.....	15
Section 1.10: Stopwatch Method.....	17
Section 1.11: Endodontic Pain Model.....	19
MANUSCRIPT.....	20
Section 1.1: Introduction.....	20
Section 1.2: Materials and Methods.....	22
Section 1.3: Statistical Analysis.....	23
Section 1.4: Results.....	24

Section 1.5: Discussion.....	32
DISCUSSION.....	36
REFERENCES.....	44

LIST OF TABLES

Table 1: Pain Intensity Measured Using a Visual Analog Scale (mm).....	31
Table 2: Time to Onset of 50% Pain Relief.....	31

LIST OF FIGURES

Figure 1: Subject enrollment flow.....	27
Figure 2: Boxplots of Pain Intensity Measurements.....,	28
Figure 3: Mechanical Pain Threshold Measurements.....	29
Figure 4: Time to onset of 50% pain relief using the Kaplan Meier Estimator.....	30

REVIEW OF LITERATURE

Section 1.1 Introduction:

Pain is a ubiquitous and multidimensional entity that varies among individuals. The International Association for the Study of Pain describes it as an unpleasant sensory and emotional experience with actual or potential tissue damage or described in terms of such damage (1). Regardless of the origin or source of the pain, it can be a debilitating problem and results in patients seeking professional advice. As dental healthcare providers, it is prudent to fully understand the prevalence, mechanisms, and treatments of odontogenic pain, acute and chronic. The prevalence of chronic odontogenic pain was calculated to be approximately 40 percent of an estimated \$80 billion spent annually on pain related health care (2). Furthermore, in a standardized survey conducted in the United States, twelve percent of households experienced acute orofacial pain within the past six months(3).

Majority of patients who present with acute odontogenic pain, manifesting as a toothache, are experiencing moderate to severe pain. In a study involving 1682 dental visits, 65% of patient's reported pain of moderate to severe intensity (4). In another study, patients (N=147) reported pain of moderate to severe pain before treatment 62.5% [moderate 15%, severe 47.5%] (5). This acute odontogenic pain results in patients seeking either emergent medical attention at a dental clinic or the hospital emergency department (ED). The number of toothache related ED visits has increased exponentially with time. This increase can be attributed to patients who lack dental insurance or who are seeking care during off hours. In a recent study, it was found that the number of visits to the ED due to toothaches for twenty to

twenty-nine year olds age group have increased to 6.1 percent within a ten year period, while there has been a 0.8 percent increase in all other causes for an ED visit (6). The problem with the increase number of visits to the ED is that an ED is able to provide only palliative care and does not address the etiology of the toothache through definitive treatment. Management of endodontic pain emergencies involves proper diagnosis, definitive dental treatment, and drugs (7). ED visits due to toothaches, since majority are not life threatening, are neither inexpensive nor considered urgent to the ED team. Patients often have long waiting periods before being seen and the treatment they receive is not definitive. Thus, it would be in the patient's best interest to avoid the ED and utilize over the counter analgesics as palliative care until he or she is able to see a dentist for definitive dental care. However, ED care should be sought if a patient is experiencing a life-threatening emergency due to pain of odontogenic origin (closing of airway or increase pressure against the orbit).

The palliative care provided by EDs consists of either prescription of medications or an incision for drainage procedure in an effort to relieve pain until a definitive treatment is performed. EDs most often prescribe analgesics or antibiotics. The three main classes of analgesics used to alleviate tooth pain are: non-steroidal anti-inflammatory drugs (NSAID), acetaminophen, and narcotics. The gold standard analgesic that has proven to alleviate dental pain is ibuprofen.

The most commonly understood mechanism of action for NSAIDs such as ibuprofen is through the reversible blockade of arachidonic acid metabolism. Arachidonic acid is a molecule present in all cell membranes throughout the body and is metabolized by an enzyme called cyclooxygenase. This enzyme has two isoforms: cyclooxygenase 1 and 2 (COX-1 and COX-2). COX-1 is constitutively expressed and has a role in homeostasis.

Tissue injury induces expression of COX-2, which results in production of inflammatory mediators that mediate pain, inflammation, and fever. Non-selective NSAIDs, such as ibuprofen reversibly inhibit COX-1 and COX-2 enzymes. Selective NSAIDs, such as celecoxib reversibly inhibit COX-2 enzymes and have no effect on COX-1. Studies have shown that the selective NSAIDs have similar analgesic benefit as compared to non-selective NSAIDs but with higher side effects, most importantly heart attacks and strokes (7). The side effects result from the inhibition of prostaglandins, which are normally responsible for platelet aggregation and vasodilation. After post-marketing surveillance, some selective COX-2 inhibitor analgesics have been removed from the market and there is an overall decrease in the use of these analgesics.

Studies indicate that NSAIDs, particularly ibuprofen, alone are effective in treating majority of endodontic pain patients. However, other classes of analgesics may be employed when NSAIDs are not effective or are contraindicated include acetaminophen and narcotics.

The mechanism of action of acetaminophen is similar to ibuprofen; it works by inhibiting COX-1 and COX-2. However, acetaminophen does not achieve the same analgesic effect as ibuprofen because a therapeutic dose is unable to inhibit COX activity when the levels of arachidonic acid are high. The absorption of acetaminophen occurs in the small intestine, metabolism in the liver, and excretion in the kidneys. The primary metabolism pathway of acetaminophen occurs by glucuronidation and sulfation. About 10% of acetaminophen is metabolized by the cytochrome 450 enzymes which produce a highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). Under normal conditions, NAPQI is metabolized by glutathione and is eliminated in the urine. When patients take more than the recommended dose of acetaminophen, the primary metabolism pathway becomes

saturated and glutathione gets depleted and patients accumulate an excessive amount of NAPQI. (8) To prevent patients from exceeding the maximum dose, FDA in 2014 has formally withdrew all prescription drug productions with more than 325 mg acetaminophen.

As aforementioned, acetaminophen does not display a strong anti-inflammatory and analgesic effect when administered at therapeutic doses. It is sometimes difficult to obtain clinical trials directly comparing specific medications. A way to overcome this problem is by utilizing the number need to treat, NNT. This is the number of patients needed to treat with medication A to achieve an improved outcome in comparison to medication B. According to The Modified Oxford League Table of Analgesic Efficacy, acetaminophen displays the highest NNT, 4.6, compared to all analgesics evaluated. However, the addition of 650-1000mg of acetaminophen or opioid Tramadol (Ultram) has been shown to enhance NSAID analgesia in both oral surgery and endodontic pain models (Cooper 1986, Breivik 2000, Doroshak 1999).

Another category of analgesics that are employed to treat odontogenic pain is narcotics. This class of drugs displays profound analgesic by activating the mu opioid receptors which prevents transmission of nociceptive signals to higher brain regions. This use of this category of drugs is limited due to its abuse potential. Most often, these drugs are used in combination with ibuprofen or acetaminophen to achieve a higher state of analgesia. The prototype narcotic is codeine.

Patient who are experiencing moderate to severe odontogenic pain are likely to take more medication than necessary to achieve analgesia. Ibuprofen has stood the test of time and is a well accepted and documented analgesic for the treatment of endodontic pain. Nevertheless, the onset of action is slow (>30.5 minutes) because the analgesic is not readily

soluble in its conventional form (9). Patients tend to supplement ibuprofen with other classes of analgesics if analgesia is not achieved in a certain time period. The adverse effects of all medications are known to be dose dependent. Thus, the higher the quantity of medication that is taken by the patient, the higher the chances that patient may experience the side effects. If patients are able to achieve pain relief faster, there will be fewer tendencies to take more medication than necessary, an increase in compliance rates, and a decrease in side effect rates.

A faster onset is desirable to the patient in pain and/or the medical professional administering the analgesic. New formulations of conventional ibuprofen known as ibuprofen salts have been introduced into the worldwide market. These include ibuprofen lysine, ibuprofen arginine, and ibuprofen sodium. Of the three, ibuprofen sodium dihydrate is the only FDA approved formulation. 7.2

In vitro studies have shown that ibuprofen sodium dihydrate has faster dissolution at pH of 1.2, 3.5 and 7.2 in comparison to conventional ibuprofen acid and ibuprofen liquigels (10).

Clinical studies conducted using the oral surgery model demonstrate that ibuprofen sodium dihydrate displays a faster T_{max} (75 minutes vs. 90 minutes for conventional ibuprofen acid), higher C_{max} (41.47 µg/ml vs. 31.88 µg/ml for conventional ibuprofen acid), and a faster onset of analgesia with the same efficacy profile as conventional ibuprofen using an oral surgery model (10-12).

Section 1.2 Pain Perception:

The manner in which an individual experiences pain is subjective, governed by many interactions including but not limited to: sex and race (13). Previous studies have reported

that women have a lower threshold of pain to noxious experimental stimuli in comparison to men (14). In addition, racial and ethnic differences can alter pain perception. A clinical trial demonstrated that African Americans found experimental thermal stimuli more unpleasant and intense than Caucasians (15-17). These differences in pain perception have underlying mechanisms that require further study. However, physicians should have no bias prior to treatment of patients from various backgrounds. It has been shown that previous physician bias has resulted in under treatment of severe pain in cancer patients of 64% Hispanic and 74% African American backgrounds (18).

A thorough understanding of the orofacial pain perception is important when trying to investigate methods of alleviating pain. Thus, a basic understanding of the peripheral and central nervous system is required. These two distinct but intertwined systems are involved in the transmission and modulation of pain.

The peripheral nervous system consists of primary afferent or sensory neurons that detect noxious stimuli. Transmission of the pain from orofacial region is performed primarily by the fifth cranial nerve, the trigeminal nerve. The cell bodies of these neurons are located in the trigeminal ganglion located in the middle cranial fossa and the axons are scattered throughout the orofacial region in areas of the skin, oral mucosa, and tooth. The primary afferent neurons can be divided into three major groups; A-delta, A-beta, and C-fibers. A-beta and C-fibers are involved in the transmission of pain while A-delta fibers are involved in proprioception and light touch under normal conditions. A-beta fibers are myelinated neurons that are involved in rapidly conducting information from non-noxious stimuli such as light touch. A-delta fibers are lightly myelinated fibers that transmit sharp pain. The C-fibers are

unmyelinated neurons that are the slowest conducting neurons that respond to mechanical, thermal, and chemical stimuli.

The central nervous system is responsible for the modulation of pain perception. The primary afferent neurons of A-delta and C-fibers synapse with second order neurons in the trigeminal nucleus, which is located in the midbrain and cervical spinal cord. The trigeminal nucleus consists of three parts: mesencephalic nucleus, chief sensory nucleus, and spinal nucleus. The respective second order neurons cross to the contralateral medulla and ascend to the thalamus via the trigeminothalamic tract. Projection neurons from the thalamus to the cortex are present for pain modulation and interpretation of pain. These projection neurons can be divided into categories: wide dynamic range and nociceptive-specific neurons, which differ by which stimuli excite the neurons. Nociceptive-specific neurons receive information from only nociceptors while wide dynamic range neurons receive information from mechanoreceptors, thermoreceptors, and nociceptors.

The perception of odontogenic pain starts with the sensory innervation neurons of pulp-dentin complex and the periradicular tissues. The primary afferent neurons involved in pulpal inflammation are C-fibers. These fibers do not respond to innocuous stimulation and result in a dull, aching, and throbbing sensation in nature. Peripheral sensitization can result in the presence of tissue inflammation. As a result, there is constant stimulation of the nerve fibers in the vicinity of the inflammation.

Section 1.3 Acute Inflammation:

The process of acute inflammation is very similar throughout the body. It consists of three different phases which have no clear dividing line and often merge together: vascular, cellular, and repair.

The vascular phase of acute inflammation results in profound changes in the local microcirculatory bed. The functional properties of the microcirculatory bed are perturbed; the regulatory systems such as sphincters in arterial vessels are altered resulting in more blood being brought into the affected area under increased pressure. Starling's Law is not in effect during this phase and there is a loss of barrier functions across vessels. Thus, there is a loss of homeostasis and plasma proteins leave the circulation and accumulate in the connective tissues. Osmolality causes an increase in swelling due to an accumulation of water in connective tissues. Mediators of vascular permeability such as histamine, serotonin, proteolytic enzymes, oxygen radicals, eicosanoids such as leukotrienes and prostaglandins, cytokines and vascular endothelial growth factors are expressed by many cells and these all play an intimate role in creating this vascular response.

The cellular phase of acute inflammation involves the innate and adaptive immunity systems. In majority of cases, the innate immune system is the first one to be activated by pathogens and is usually sufficient to clear the infection. However, when the innate immune system is overwhelmed, it triggers and directs the adaptive arm, thus activating specific B and T cells for pathogen clearance. Innate immunity is characterized by its ability to recognize a wide range of pathogens such as viruses, bacteria, and fungi, but through a limited number of germline-encoded receptors, which are expressed, on mast cells, macrophages, monocytes, dendritic cells and neutrophils. White blood cells leave the microcirculation and move into the interstitial connective tissues. These cells move into the connective tissue because of adhesion molecules such as selectins (P, E, and L) and integrins. Through a process referred to as diapedesis, there is a migration of leukocytes through the endothelium after adhesion. Leukocytes transverse the endothelium towards the infecting

organism through a process called chemotaxis. In most forms of acute inflammation, neutrophils predominate the inflammatory infiltrate during the first 24 hours and then are replaced by monocytes in 24 to 48 hours.

The last phase of acute inflammation is referred to as repair phase, or resolution of inflammation. Once the leukocytes enter tissues, they gradually change their major lipoxygenase derived products to lipoxins. Cell to cell interaction between activated platelets and neutrophils provide a major source for lipoxin A₄ and B₄. Platelets produce these mediators from an intermediate derived from neutrophils. Lipoxins play an active role in resolving the inflammatory response. They bind to specific cell surface receptors on neutrophils to inhibit chemotaxis and superoxide generation. They also promote neutrophil apoptosis. By contrast, lipoxins promote monocyte chemotaxis but induce phagocytosis of apoptotic neutrophils. Lipoxins do not induce cytokine production by monocytes/macrophages. The body is able to protect and heal itself from injury using this acute inflammation model.

Section 1.4 Symptomatic irreversible pulpitis:

The process of acute inflammation that occurs in the pulp following tissue injury is similar to acute inflammation described above; however, the key difference is that the human pulp tissue is contained within a hard encasing made up of dentin. This restricts the tissue from expanding during inflammation. If the noxious stimulus is not removed or is severe, the low compliant environment of teeth can result in painful acute pulpitis leading to necrosis of the pulp.

The human pulp is a resilient tissue that has many defense mechanisms, both physical and chemical. The most common etiology for pulpal pathology is dental caries. The dental

literature has demonstrated that there is a histological change in pulp even without cavitation in the enamel. The histological changes become more debilitating as the carious front approaches the pulpal tissue (19, 20). There are defense mechanisms that help prevent the pulp tissue from undergoing necrosis. The dental pulp's first line of defense is dentin sclerosis, which results from deposition of intratubular dentin and direct deposition of mineral crystals into narrowed tubules (21). The second line of defense consists of reparative dentin, a disorganized dentin layer that is laid down as a result of noxious stimuli to dentin. The third line of defense consists of humoral and cellular pulpal immune responses.

The innate immune response is mediated by resident cells on the periphery of the pulp such as odontoblasts. These cells recognize pathogen-associated molecular patterns (PAMPs) on invading microorganisms, proinflammatory cytokines, chemokines, or antimicrobial peptides using specific receptors called pattern recognition receptors (PRRs). One class of PRRs include toll like receptors (TLRs) (22). A inflammatory cascade is initiated once PRRs recognize PAMPs; consisting of opsonization, activation of complement cascades, phagocytosis, activation of proinflammatory pathways, with an initial influx of neutrophils (22). Neuropeptides also play a role in pulpal inflammatory. These include but are not limited to substance P, calcitonin gene-related peptide (CGRP), neurokinin A (NKA), NKY, and vasoactive intestinal peptide (VIP). These peptides are involved in vasodilation, increasing vascular permeability, chemotaxis and stimulatory agents for macrophages and T lymphocytes. Furthermore, stimulation of Substance P can result in increased production of arachidonic acid metabolites. However, Substance P and CGRP are also involved in mitogenic activity of pulpal and odontoblast-like cells that result in tertiary dentin (23).

If the noxious stimulus is not removed, this innate immune response turns into a

humoral and cellular response. Chemical mediators such as IL-8, TFG-B1 result in an increase in the number of inflammatory cells, in particular dendritic cells (24). The resident dendritic cells, CD11c+ and F4/80+, are responsible for recognizing and presenting antigens to T lymphocytes (25). In addition, odontoblasts have been involved in humoral immune response to caries.

Once the carious front reaches a particular level, 1.5 mm from the pulp, there is an acute exacerbation of the immune response, which results in an influx of neutrophils (26, 27). Continual pulpal inflammation results in microabscesses in the pulp. With time these abscesses coalesce which results in pulpal necrosis from the coronal portion of the pulp down to the apical segment. In an attempt to destroy the invading microorganism, the innate and adaptive immune responses result in destruction of the pulpal tissue.

Section 1.5 Symptomatic Apical Periodontitis:

The acute inflammation in periapical tissues follows a similar course as the pulpal tissue. The goals of the acute apical periodontitis are to remove the microbial agents, recruit more inflammatory cells such as neutrophils and macrophages in an effort to neutralize and degrade the microbes and toxin byproducts that are present.

It was once postulated that apical periodontitis only resulted after complete pulpal necrosis has occurred in the dental pulp. However, more recent studies have discovered that apical periodontitis can develop well before pulpal necrosis (28, 29). Neuronal sprouting has been shown to be present in the periapical area three to five weeks after irreversible pulpitis (30). In addition, an influx of osteoclasts and bone destruction has been demonstrated before pulp necrosis. (31). Toxins and metabolic byproducts that egress from the pulp canal space can illicit an inflammatory reaction very similar to the one in the dental pulp. Toxins such as

lipopolysaccharide (LPS) and lipoteichoic (LTA) are able to stimulate sensory nerve fibers to release neuropeptides such as Substance B and CGRP, which are able to cause vasodilation and vascular permeability, respectively (32, 33). In addition, LPS has shown to cause pain, while LTA has been shown to stimulate leukocytes to release inflammatory mediators such as IL-1, IL-6, IL-8, TNF- α , and prostaglandin E2 (34). TLRs on neutrophils, NK cells, dendritic cells, phagocytes, and B-lymphocytes are able to recognize any PAMPs in the area and induce cellular differentiation.

Adaptive immunity entails both a cellular and humoral response. The cellular components consist of T-cells and B-cells. T cells interact with antigens when presented by MHC class II molecules while B cells interact with antigens directly. After CD4 T cells are stimulated by antigens, they differentiate into T helper cells. T helper cells differentiate into TH1 and TH2. TH1 are responsible for producing IL-2 and interferon- γ , which activates macrophages and B cells to produce opsonizing antibody while TH2 produces IL-2, -5, -10 and -13, which activates B cells to produce a neutralizing antibody. As with acute inflammation in any part of the body, there is a release of neuropeptides such as CGRP and Substance P upon stimulation of afferent nerve fibers. Substance P also increases the secretion of IL-1, TNF- α , IL-6 from macrophages, T-cell proliferation and enhances antigen induced INF- γ by T-cells (35).

If the pathological insult is not removed, the innate and adaptive immune response will result in bone destruction. Bone remodeling takes place throughout life, and there is a constant balance between bone destruction and bone regeneration. In apical periodontitis, this balance shifts towards an increase in bone destruction due to the inflammation that is present in the surrounding tissues. The cells that are involved in bone destruction are osteoclasts,

which differentiate from osteoclast precursor cells from the monocyte-macrophage lineage of cells in the bone marrow as a result of different chemical mediators in the body. Osteoclasts are the cells that are responsible for bone degradation. The activation of the RANK pathway by RANKL results in differentiation of the osteoclast progenitor cells. RANKL is produced by proinflammatory cytokines IL-1, IL-6, TNF-alpha, bone stromal cells, and T-cells. It can also be produced by osteoblasts, which are stimulated by PTH hormone. Once attached to mineralized bone, osteoclasts form a ruffled border and use an ATP pump to create and acidic environment that will resorb the underlying bone. Osteoclast activity is balanced by osteoblasts that produce osteoprotegerin (OPG), which resorbs the RANKL and stop the osteoclast differentiation pathway. (36-40)

Conventional periapical radiographs are utilized to determine the amount of bone destruction. In acute symptomatic apical periodontitis, no radiographic signs of bone destruction are usually present. There may be a widened periodontal ligament space with some destruction of the lamina dura. Radiographic signs will appear if the microbial insult continues and are usually present in chronic symptomatic apical periodontitis and chronic apical abscess.

Section 1.6 Mechanical Allodynia:

There is a lack of correlation between clinical and histological findings at both the pulpitis and apical periodontitis level. Radiographically, there is usually lack of periapical bone destruction but the tooth may display slight widening of the periodontal ligament space and loss of lamina dura space. Nerve sprouting of sensory nerve can increase the receptive field size of teeth experiencing acute apical periodontitis (30). Furthermore, due to the continued really presence of inflammatory mediators, peripheral and central sensitization can

occur in periradicular tissues. This can result in a constant firing of afferent sensory neurons. Patient can experience allodynia or hyperalgesia. Allodynia is defined as sensitivity to innocuous mechanical or thermal stimuli and hyperalgesia is defined as hypersensitivity to noxious mechanical or thermal stimuli.

Mechanical allodynia is defined as a decrease in mechanical threshold. It is usually defined as pain due to pressure or biting and is tested with percussion testing using the back of a mirror handle (41). It was generally thought that hyperalgesia, an exacerbated response to cold, is attributed to pulpal disease while mechanical allodynia, pain to pressure or biting, is attributed periradicular disease. However, a clinical study has found a correlation between hyperalgesia and mechanical allodynia. This study found that the incidence of mechanical allodynia in patients with irreversible pulpitis was 57.2% (41).

There are three possible hypotheses explaining how patients with irreversible pulpitis can experience mechanical allodynia. 1) activation of mechanoreceptors in the pulp 2) activation of periradicular mechanoreceptors via egress of inflammatory mediators and bacterial toxins 3) central sensitization via pulpal nociceptors (41).

Section 1.7 Measuring pain in patients:

Since pain perception is a complex entity, multiple evaluation tools are needed to fully understand it. These methods should either quantitative or qualitative, or both. A review of the pain literatures offers insight on objective tools, which have stood the test of time.

Section 1.8 Measuring symptomatic apical periodontitis:

Irreversible pulpitis is often characterized by spontaneous pain and an exaggerated, lingering response to a thermal stimulus. The underlying mechanism is thought to be activation of pulpal nociceptors (pain-sensing neurons) by local inflammatory mediators.

Teeth with an irreversibly inflamed pulp may have normal or inflamed periapical tissues (apical periodontitis). A prior study reported that more than 50% of teeth diagnosed with irreversible pulpitis also have symptomatic apical periodontitis (41). Symptomatic apical periodontitis is diagnosed by a decrease in mechanical pain thresholds (mechanical allodynia), which has been traditionally been measured by using the back of a mirror handle (Cohen 2002). However, a newer method of quantifying mechanical allodynia consistency is by using a Bite fork Force Transducer (42). This instrument has been tested in both in vitro and in vivo trials (42, 43). It consists of a bite fork that was modified by attaching a tooth sleuth head that acts as an occlusal guide. This fork can measure forces up to 1,000 N. However, forces of 777 N are considered the maximum limit that prevents damage in normal teeth (44). Another benefit of using this instrument is that the investigator of the trial is able to use the patient's contralateral tooth as a control. Previous studies demonstrated that a patient that presents with symptomatic irreversible pulpitis and symptomatic apical periodontitis displays mechanical allodynia, a reduction in pain threshold, by 77% on the affected tooth compared to the contralateral tooth, allowing this tooth to serve as a control (41).

It has been proposed that patients who are experiencing moderate to severe pain will often premedicate themselves before presenting to the dental office, which can make diagnoses difficult. A study has shown that ibuprofen masks about 25% mechanical allodynia in patients presenting with symptomatic irreversible pulpitis and symptomatic apical periodontitis. It is unable to completely mask mechanical allodynia, making the bitefork force transducer a reliable tooth for pain studies (45).

Section 1.9 Visual Analog Scale:

Since pain is a multidimensional entity, it is important to get an accurate representation of the patient's pain characteristics. There are many methods of obtaining pain ratings that include numerical rating scale, verbal rating scale and visual analog scale.

Numerical rating scale consists of an 11, 21, or 101 point scale, with anchors of no pain or worst pain. This method can be delivered to the patient verbally or graphically. The verbal rating scale is a categorical scale which includes words such as none, slight, moderate, and severe pain. This method is delivered to the patient verbally.

Visual analog scale consists of a continuous line, of varying lengths (11, 21, or 101mm), with anchors of no pain and worst pain imaginable. (46) This method can be delivered to the patient on paper or electronically. If a paper method is utilized, it is imperative to not make photocopies, as this can shift the 100mm scale length (47, 48). The orientation of the scale, vertical or horizontal, needs to be addressed depending on the group of subjects being evaluated. With English language speakers, a horizontal scale results in less failures than a vertical scale (49). The visual analog scale has been demonstrated to be highly reproducible, with correlation coefficients ranging from 0.97 to 0.99 (50, 51). A study conducted on patients experiencing acute pain concluded if the visual analog scale is repeated by the same individual in a short time frame, the two responses will be within 2mm of one another 50% of the time, 90% within 9mm, and 95% within 16mm (50).

Much research has been conducted in determining what kind of continuous scale would lead to accurate representation of the patient's pain. A study has shown that a 5 cm scale gives inconsistent responses when compared to 10, 15 or 20 cm scales (52). In addition, this study concluded that patients are able to reproduce the visual analog rating mark of constant painful stimulus and any changes in rating signifies real changes in opinion.

Additional studies have been conducted to address sufficient amount of length of a VAS - whether it is beneficial to have an 11, 21, 101-point scale. Study by Jensen et al indicates that an 11-point scale is sufficient in evaluating pain. Approximately 75% of patients used the 101-point scale as if it had 11 points. However, a 101-point scale is able to provide more discrimination when evaluating pain (53).

Even though the VAS is the most robust test for pain rating, it does have some drawbacks. From a patient's perspective, a VAS is more complicated method than a VRS or NRS. Older, children and cognitively impaired subjects are unable to properly complete the VAS. In addition, there is a 20% in variability if VAS is reproduced by a subject who is experiencing a continuous stimulus. This study concluded that the actual experience of pain varied over time even though the stimulus did not change (54). With all things considered, a VAS is a highly sensitive test which can detect small changes in pain if performed correctly.

Numerical rating scale has shown poor reproducibility (55). A verbal rating scale is the least sensitive of the three pain rating scales and this leads to either an underestimation or overestimation of pain. There is not much correlation between the different pain rating scales (46). For example, a 30mm on a VAS is not equivalent to 3/10 on NRS. Investigators should be mindful when trying to employ more than one pain rating scale to understand a patient's pain level.

VAS score of 30 on 100mm pain indicates moderate pain and score of 54+ indicates severe pain in ACUTE pain patients (56). In another study, Briggs and Closs found that cancer patients classified 35mm on VAS scale as severe pain (57)

Section 1.10 Stopwatch Method:

Historically in pain clinical trials, the onset and duration of action was measured at set time intervals. This type of data collection on onset and duration of action has inherent flaws. There is a lack of sensitivity and standardization among patients. For example, if patient A is given medication X and patient B is given medication Y. Baseline measurements of pain are established and patients are stopped every 30 minutes to evaluate the onset and duration of pain. Hypothetically, if medication X starts working at 20 minutes and medication Y starts working at 25 minutes but has higher analgesic components. At the first thirty-minute time point, both patient A and patient B will state their respective medications have provided relief. The same scenario can be applied when measuring the duration of the medication. This type of data collection is unable to pick apart very discreet differences between analgesics, which is essential when determining the onset and efficacy of a certain medication.

To alleviate this issue, a continuous time scale is needed, in which patients are able to tell the investigators exactly when in the trial the pain relief occurred. Thus, a stopwatch method has been employed in many analgesic studies. This has proven to be a very sensitive method in providing accurate onset and duration of action of analgesics (58-60).

Studies utilizing the stopwatch method often instruct patients to stop time when they feel meaningful pain relief. In a migraine study, patients were instructed to complete an ordinal scale as well as utilize the stopwatch. The meaningful pain relief time was correlated to the ordinal pain rating scale: at this particular time, the 5-point ordinal scale ratings were: 17% complete relief, 45% a lot of relief, 25% with some relief, and 12% with little relief (58). In another study, subjects were informed to stop time when they felt meaningful pain relief, which may come before complete pain relief (60). This study also concluded that the

stopwatch is a sensitive tool and it provides information that would otherwise be unattainable from ordinal scales.

Section 1.11 Endodontic pain model:

An oral surgery pain model does not replicate an endodontic pain model. Thus, the information obtained from clinical trials using the oral surgery pain model cannot be directly applied to pain from endodontic origin. An oral surgery pain model employs patients who are young and healthy with mild or no pre-operative pain. The patients undergo an elective surgery procedure and the trauma from the surgery is the source of inflammation. Neither is this inflammation present prior to the elective procedure, nor is it of bacterial origin. The patients are given the analgesic to address inflammation from trauma. An endodontic pain model employs patients who vary considerably in health and age. There is pre-existing bacterial infection that results in inflammatory reactions taking place prior to the analgesic being administered. The pre-existing inflammation from a bacterial insult in the endodontic pain model is the key distinction between the two models.

To our knowledge, no studies have been conducted using ibuprofen sodium dihydrate to determine its ability in reducing odontogenic pain associated with infection of a vital pulp. Our null hypothesis is that ibuprofen sodium dihydrate provides faster and more efficacious pain relief compared to conventional ibuprofen acid formulation in endodontic pain patients.

MANUSCRIPT

Section 1.1 Introduction:

Odontogenic pain is a multidimensional entity (3). It usually has an acute onset of moderate to severe pain intensity (4, 5, 61, 62). In a study evaluating the self management of odontogenic pain, only half of the individuals attempted to contact a dental professional and sixty-four percent used over-the-counter (OTC) analgesics instead (63). A similar finding from another retrospective study concluded that between eighty-one to eighty-three percent of individuals used OTC analgesics for odontogenic pain (28). First-line OTC analgesics used for pain relief include the following: aspirin, acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDs).

Ibuprofen acid has been used for decades to alleviate odontogenic pain and is considered the gold standard NSAID in clinical trials (64, 65). A distinct disadvantage of this analgesic is that it is not readily soluble (10, 66). The solubility of an analgesic determines its serum levels, which, in turn, determines the onset and the extent of the analgesic effect (10). A decrease in solubility therefore results in a delayed onset of action. In studies examining pain relief for migraines, rapid pain relief is one of the most important priorities for both the patients and clinicians (67). Patients are likely to use more than the recommended dose of an analgesic, or to supplement it with a different class of analgesic, when rapid pain relief is not achieved. This can be detrimental since adverse effects are dose dependent.

Enhancements in ibuprofen acid's pharmacokinetics have led to the development of ibuprofen liquigels and ibuprofen salts such as lysine, arginine, and sodium dihydrate. Of the three salt formulations, only ibuprofen sodium dihydrate is currently tablet formulation approved by the United States Food and Drug Administration (68). An in vitro study demonstrated a faster dissolution of ibuprofen sodium dihydrate at a pH of 1.2, 3.5 and 7.2 in comparison to ibuprofen acid and ibuprofen liquigels (10). This greater solubility allows greater absorption and subsequently, a faster onset of analgesic effect. In vivo pharmacokinetic studies using the oral surgery model demonstrated that ibuprofen sodium dihydrate has a higher drug plasma concentration, C_{max} , (41.47 $\mu\text{g/mL}$ vs 31.88 $\mu\text{g/mL}$) and a lower time to reach C_{max} , i.e. T_{max} , (75 minutes versus 90 minutes) than ibuprofen acid (10, 11), thereby producing faster and more profound analgesia (69).

The data from the oral surgery model, although useful for understanding acute pain, is not readily translated to endodontic pain. In the oral surgery model, the study subjects often presented with either no pain or mild pain prior to the removal of their third molars. Thus, the acute inflammatory pain evaluated in such clinical trials results mostly from the surgical trauma. In contrast, pain associated with a pulpal and/or periapical pathology in the endodontic model is thought to result from a preexisting, often chronic, polymicrobial infection. At this time, the analgesic efficacy of ibuprofen sodium dihydrate in endodontic pain is unknown.

The objective of this study is to compare the level of pain relief, the change in mechanical allodynia, and the time to onset of 50% pain relief from a single-dose of ibuprofen sodium dihydrate to that from a comparable dose of ibuprofen acid in patients with symptomatic irreversible pulpitis and symptomatic apical periodontitis.

Section 1.2 Materials and Methods:

This is a randomized, double-blinded, and controlled clinical trial. This study was approved by the Institutional Review Board of The University of North Carolina Chapel Hill. Healthy men and women (aged 18-60 years old) experiencing moderate to severe dental pain from a single tooth with a pulpal diagnosis of symptomatic irreversible pulpitis, defined as spontaneous pain and lingering response to thermal stimuli, and periapical diagnosis of symptomatic apical periodontitis, defined as sensitivity to percussion, were recruited for the study. Subjects who used any type of analgesics in the preceding six hours were excluded from the study, as were subjects who had taken analgesics that have an analgesic effect of larger than six hours. Subjects with hypersensitivity or allergy to NSAIDs, gastric and/or duodenal ulcer, and gastrointestinal bleeding were excluded from the study. Pregnant and lactating women, and subjects classified as American Society of Anesthesiologists Class III through V were also excluded. Written informed consent was obtained from all subjects.

The dental examination was performed by one examiner (T.T). The pulpal diagnosis was determined with Endo Ice (Coltene Dental). The periapical diagnosis was determined by tapping the teeth with the back of a mirror handle. Subjects were asked to report pain by raising his or her hand. Both the painful tooth and the contralateral asymptomatic (control) tooth were examined in this manner. Baseline pain intensity was determined by using a 100 mm visual analog scale with anchors of 0 mm, representing no pain, and 100 mm, representing the worst pain imaginable (70, 71). A reading of more than 30 mm on the visual analog scale was considered moderate in intensity (56, 57). Mechanical pain threshold was measured on the painful and the contralateral asymptomatic (control) teeth using a digital bite force transducer ((43, 45). It has an intraobserver reliability of 0.63-0.68 and

interobserver reliability of 0.3-0.64. Subjects were given a standardized set of instructions: *“I am going to place this bite fork between your upper and lower teeth to measure how hard you are able to bite. I will place the bite fork against your upper tooth and then I would like you to close and gently rest your teeth together on this bite fork. When I signal you, increase biting pressure slowly until you are exerting as much force as possible and release immediately when you feel discomfort or pain. Other patients have described the feeling they have on maximal biting as a pinch, tingle, or strong pressure feeling. The bite force measurement from the time I signal you to start until you open should take approximately five seconds”* (42). Mechanical allodynia was defined as the difference in mechanical pain thresholds between the control and the affected teeth (42)..

Subjects received a single dose of 400 mg (2 tablets x 200mg) ibuprofen acid tablets (Advil[®], Madison, NJ) or an equivalent dose of 512 mg (2 tablets x 256mg) ibuprofen sodium dihydrate tablets (Advil[®], Madison, NJ). Randomization was performed by a third party prior to the study. The study examiner left the operatory before the patient was instructed to take the medication, following which a stopwatch was started. Subjects were instructed to stop the stopwatch when they felt a 50% decrease in pain intensity. Subjects were also instructed that the stopwatch did not need to be stopped if no such stated pain relief was experienced. At 60 minutes, the following final measurements were taken: pain intensity rating of the painful tooth, and mechanical pain thresholds of the painful and control teeth.

Section 1.3 Statistical analysis:

There were three outcome variables for this study. The decrease of pain intensity and change in mechanical allodynia was analyzed by fitting a linear mixed-effects model (LMM) to data, via Restricted maximum likelihood (REML). All the statistical analysis was

performed in R statistical software (version 3.2.3, www.cran.r-project.org). The R function lmer in the package lme4 was used for this mixed-effects model, in which the subjects IDs are considered as the random variable to affect the intercept of the regression. The effects of the three outcomes are considered as fixed effects. The onset of 50% pain relief was analyzed using the Kaplan Meier Estimator as in survival analysis.

Comparisons were made of control and affected teeth between pre-administration and post-administration of drug within the 60-minute study period. The effects due to the usage of the different drugs are inferred based on these comparisons. Due to the usage of the mixed effect model, all analysis considered the data as paired data by the subject IDs.

After checking the boxplot, histogram and QQplots of the KN scores of pain intensity, the scores were log2 transformed for a more symmetrical distribution so that the assumptions of the models are valid. The clinic impact of the scores may be transferred back to the original scale.

Other possible confounders include age and gender. We have checked the association between these two confounders and the two outcomes respectively.

Significance was set at ($P < 0.05$). Marginal Significance was set at ($P = 0.05-0.1$).

Section 1.4 Results:

This study enrolled subjects who had scheduled appointments with the Urgent Care Clinic at the University of North Carolina School of Dentistry, Chapel Hill, NC (Figure 1). A total of 2,415 appointments were scheduled in an eleven-month period from March 2015 to February 2016. An attempt was made by the study examiner to contact 1,455 individuals that met the age inclusion criteria. Of those individuals, 749 could be reached and an initial phone interview was conducted to determine eligibility for the study. A clinical exam was

completed on 86 individuals to ensure all inclusion criteria were met. 41 subjects were enrolled and completed the study. The cohort comprised of 23 females and 18 males. The age range was 19 to 59 years old. The median age was 33 years old. All subjects completed the study.

Mixed effect linear model (REML) was used to measure a decrease of pain intensity (Figure 2 and Table 1). Pain intensity was calculated by the following equation:

$$\frac{(\text{Pre-administration pain intensity} - \text{Post-administration pain intensity})}{\text{Preoperative pain intensity}} \times 100$$

There was a 50.8% decrease in pain intensity following the use of ibuprofen sodium dihydrate ($P < 0.001$). There was a 33.3% decrease in pain intensity following the use of ibuprofen acid ($P < 0.001$). The ibuprofen sodium dihydrate group displayed greater than 18% decrease in pain intensity in comparison to ibuprofen acid group ($P < 0.05$).

Restricted maximum likelihood (REML) was used for analysis of change in mechanical pain thresholds. Data was normalized using log to the power of two (Figure 3). There was no statistical difference in the pre-administration values of control and painful teeth in the ibuprofen acid and ibuprofen sodium dihydrate groups. Thus, the pre-administration data from all control teeth (ibuprofen and ibuprofen acid groups) was combined to form one pre-administration control teeth group and the pre-administration data from all affected teeth (ibuprofen and ibuprofen acid groups) was combined to form one pre-administration affected teeth group. Mechanical allodynia was calculated by the following equation:

$$\frac{(\text{Deltas of control tooth} - \text{Deltas of affected tooth})}{\text{Deltas of control tooth}} \times 100$$

There was a 15% difference in the change of mechanical allodynia ($P<0.05$) in the ibuprofen sodium dihydrate group and a 9% difference in the change of mechanical allodynia in the ibuprofen acid group ($P>0.05$).

A Kaplan-Meier Estimator was used for analysis of onset of 50% pain relief. This test measured the survival function of the data set. The median time to onset of 50% pain relief in the ibuprofen sodium dihydrate group was 26.5 minutes as compared to 44.0 minutes in the ibuprofen acid group (Figure 4 and Table 2) ($P=0.08$). In addition, there were more patients that did not achieve the onset of 50% pain relief within the sixty minutes trial period in the ibuprofen acid group ($n=8$) as compared to the ibuprofen sodium dihydrate group ($n=4$).

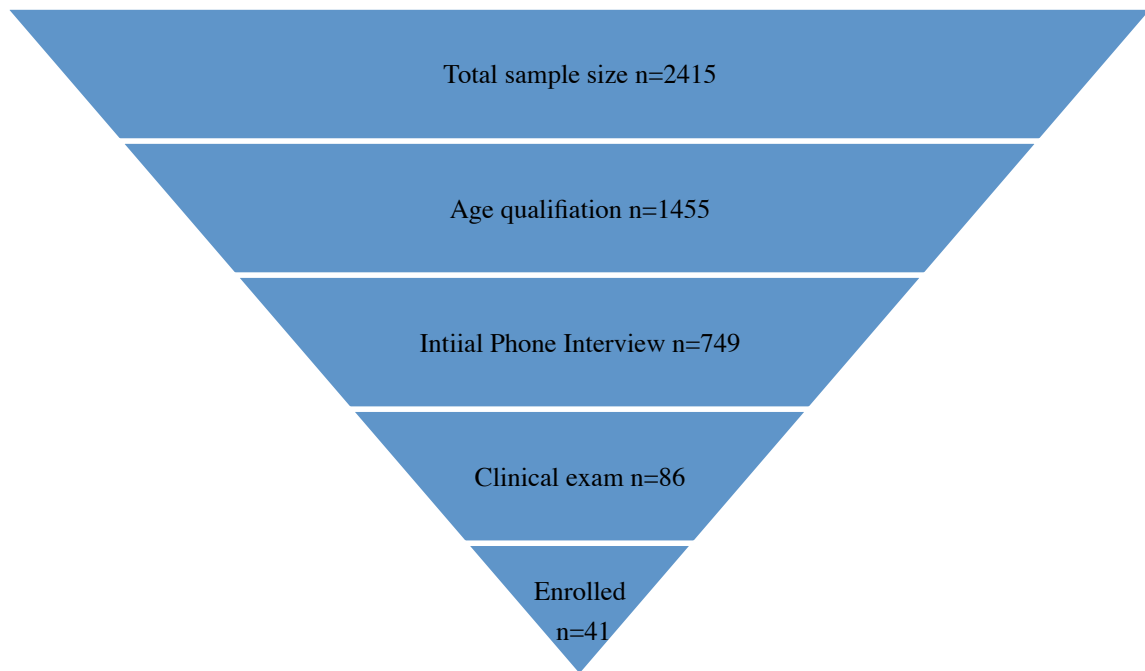


Figure 1: Subject enrollment flow. 2,415 patients were scheduled in the urgent care clinic at the University of North Carolina School of Dentistry, Chapel Hill, NC from 3/2015-2/2016. An attempt was made to contact 1,455 patients that met the age inclusion criteria (18-60 years old). Phone interviews were conducted with 749 patients followed by invitation to a clinical exam to determine study eligibility. Out of 86 patients who presented for a clinical examination, 41 patients met all inclusion criteria and were enrolled into the study.

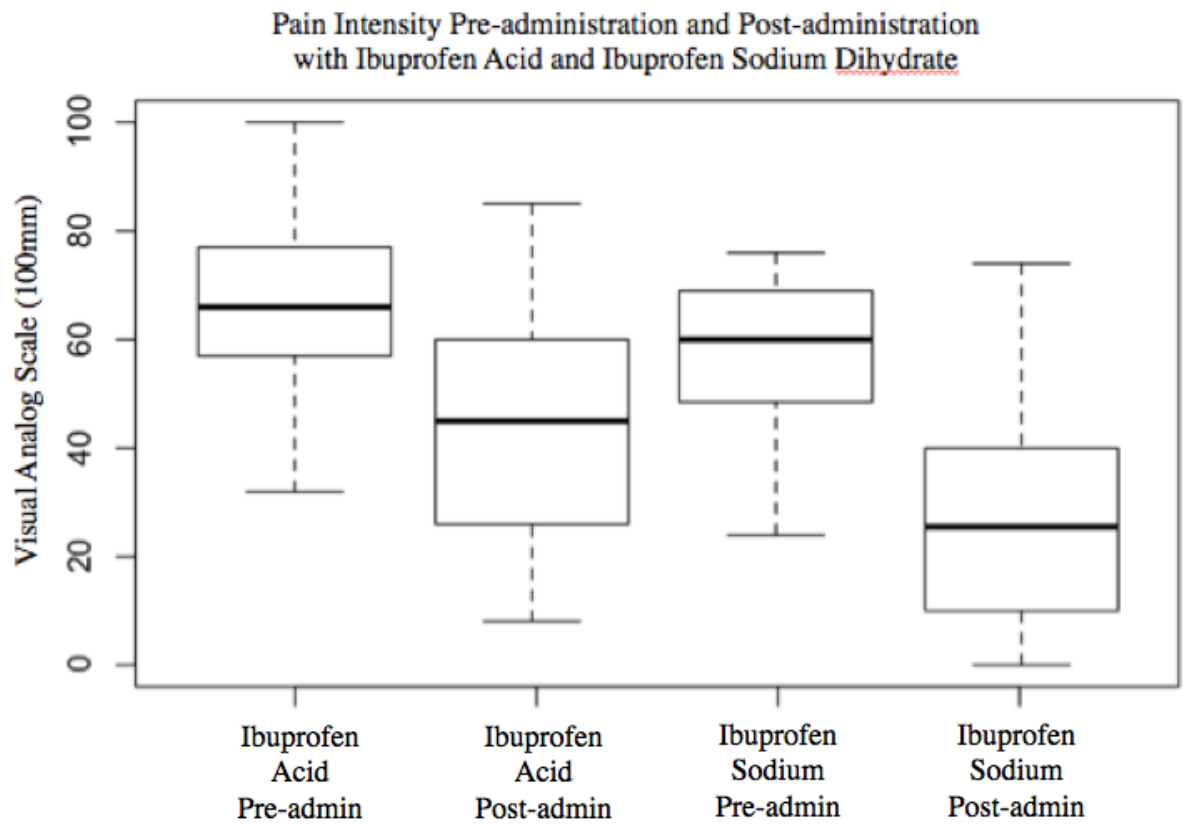


Figure 2: Boxplots of Pain Intensity Measurements

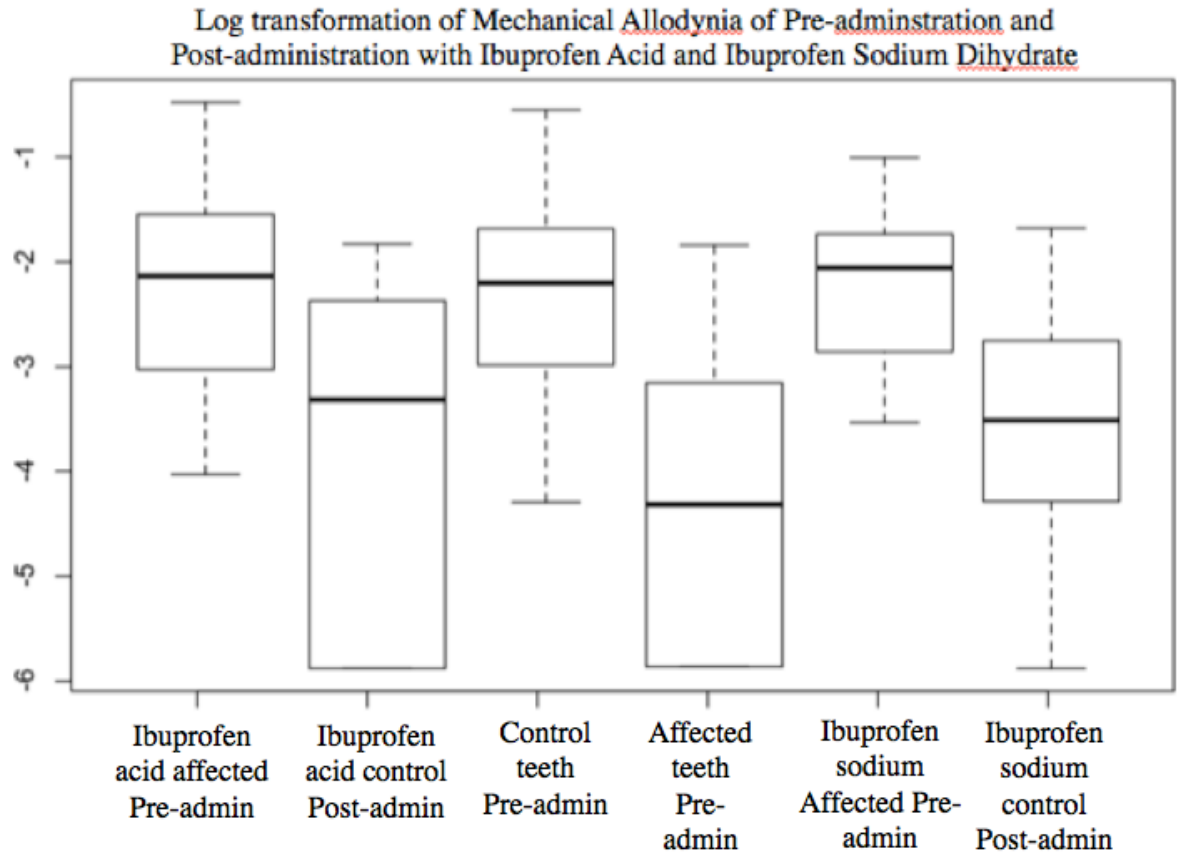


Figure 3: Mechanical Pain Threshold Measurements. Log transformation of Mechanical Allodynia of of Pre-administration and Post-administration with Ibuprofen Acid and Ibuprofen Sodium Dihydrate in order to normalize data. All control teeth from ibuprofen and ibuprofen sodium dihydrate were grouped together as “control teeth pre-administration”. All affected teeth from ibuprofen and ibuprofen sodium dihydrate were grouped together as “affected teeth pre-administration”. Larger variance can be seen in the ibuprofen acid affected post-administration group ($P>0.05$). Ibuprofen sodium affected group post-operative showed a statistically significant difference ($P<0.05$).

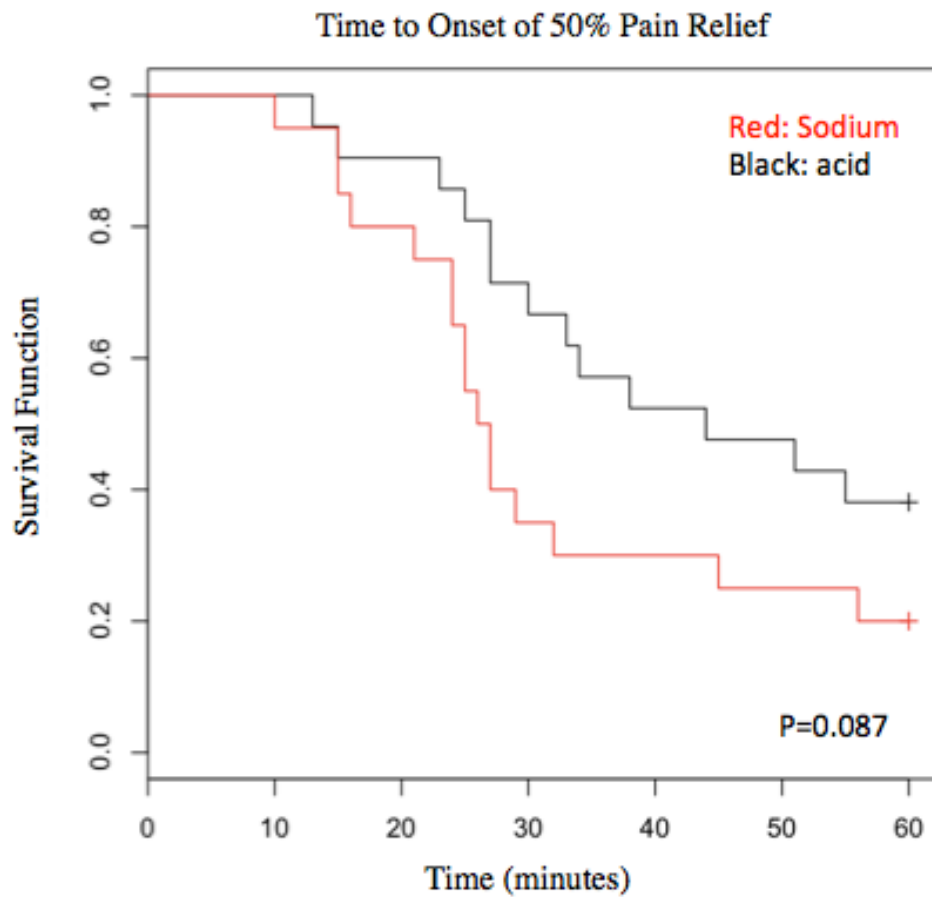


Figure 4: Time to onset of 50% pain relief using the Kaplan Meier Estimator. Ibuprofen sodium dihydrate administration resulted in 17.5 minutes faster onset of pain relief of 50% than administration of ibuprofen acid (P=0.08).

	Estimated Standard (mm)	Standard error of the mean (mm)
Ibuprofen Acid Pre-operative	64.95	4.158
Ibuprofen Acid Post-operative	43.33	4.158
Ibuprofen Sodium Dihydrate Pre-operative	56.95	4.261
Ibuprofen Sodium Dihydrate Post-operative	28.00	4.261

Table 1: Pain intensity measured using a Visual Analog Scale (mm)

	Total	# of subjects with 50% pain relief	Median time to 50% pain relief (min)
Ibuprofen Acid	21	13	44.0
Ibuprofen Sodium Dihydrate	20	16	26.5

Table 2: Time to Onset of 50% Pain Relief

Section 1.5 Discussion:

The results of this study suggest that the administration ibuprofen sodium dihydrate resulted in significantly greater reduction in pain intensity, faster onset of pain relief, and greater reduction in mechanical allodynia than the administration of ibuprofen acid in acute endodontic pain

In this study, both ibuprofen acid and ibuprofen sodium dihydrate groups reported a statistically significant decrease in pain intensity. This finding is in agreement with previous studies that have evaluated the two formulations using the oral surgery model (12, 72). Moreover, ibuprofen sodium dihydrate group reported an 18% greater decrease in pain intensity than ibuprofen acid group, which may reflect the faster dissolution rate of the former, and, in turn, a larger bioavailability.

A fast onset of pain relief is an important feature of any analgesic (67). Subjects in the ibuprofen sodium dihydrate group experienced a median onset of 50% of pain relief which was 17.5 minutes faster than the ibuprofen acid group. Although this result did not reach the level of statistical significance set at $P < 0.05$, it was very close. Future larger cohorts may determine otherwise. The faster onset of action may indirectly translate longer duration of pain relief (69). Therefore patients will be less likely to take more than the recommended dose of analgesics medication, and correspondingly a decrease in events. We did not actively elicit adverse effects experienced by the cohort in this time-limited trial of a single dose analgesic. Neither did any of the subjects report any adverse effects if experienced.

A number of individuals in both groups did not achieve 50% pain relief within the sixty-minute trial. However, the percentages of subjects (38% of subjects in the ibuprofen acid group and 20% of subjects in the ibuprofen sodium dehydrate group) not achieving 50%

pain relief within 60 minutes is consistent with the previous oral surgery model study that had a larger sample size (n= 198 in each group) (12). It is important to realize that while ibuprofen is an effective analgesic for acute odontogenic pain, not all patients respond to it. Some reasons for the lack of response to ibuprofen between patients may include different gene expression and functional polymorphisms of the COX2 gene (73). This subset of patients may require an additional class of analgesic to achieve pain relief.

This study is the first to report changes in mechanical pain thresholds of painful teeth following the administration of an analgesic. Mechanical allodynia is a decrease in the mechanical pain threshold as a consequence of peripheral and central sensitization (41). The statistically significant change in mechanical allodynia in the ibuprofen sodium dihydrate group was 15% after sixty minutes of administration. Since this study was concluded at sixty minutes, there is a possibility that not enough time had lapsed for the analgesic to affect the central sensitization component of mechanical allodynia. A larger difference in mechanical allodynia may have been found if the study was extended to more than one hour. The study was concluded at sixty minutes because individuals enrolled in the study presented to the dental school in acute odontogenic pain. We felt that it would not be ethical to keep the non-responders in pain for longer than the normal diagnostic period.

This is the first study comparing the analgesic effects of ibuprofen acid and ibuprofen sodium dihydrate in an endodontic pain model. Most studies about the use of analgesics in the endodontic literature focus on its effect on postoperative pain or on it as an adjunct to obtaining profound local anesthesia. Based on these studies, the current recommendation for pain relief includes the use of 600mg ibuprofen or a combination of 650mg ibuprofen with 1000 mg of acetaminophen for pain relief (64, 65). It is important to note that the dose used

in this study for both ibuprofen formulations is significantly lower than the current recommended dose. We decided to use 400mg of ibuprofen acid and an equivalent dose of 512 mg of ibuprofen sodium because this dose has produced 56% pain relief in patients with acute inflammation(74). A dose higher than 400mg would result in a possible ceiling effect and it would become difficult to see any differences between the two formulations. It can be inferred that the current recommended dose of ibuprofen acid (600mg) if translated to ibuprofen sodium dihydrate (768 mg) could potentially have a larger decrease in pain intensity, a larger change in mechanical allodynia, and possibly a faster onset of action. The results from this study suggest that the oral surgery model and the endodontic model have similar results when evaluating the decrease of pain intensity and the onset of 50% of pain relief.

There are inherent challenges within the endodontic pain model that make it difficult to recruit subjects for the study. One such challenge is that subjects are often in moderate to severe pain and tend to pre-medicate with analgesics prior to their dental appointments. In this study, the strict inclusion and exclusion criteria, as well as, the inability to contact many individuals prior to their dental appointments resulted in a small sample size. In addition, a future study may benefit from using a double stopwatch method in which an individual is asked to stop one stopwatch at the first sign of pain relief and stop a second stopwatch when meaningful pain relief is achieved (60, 75). This method would ensure that the patient is reporting meaningful pain relief and not merely just the onset. If the patient does not stop the second stopwatch then it could be concluded that proper analgesia has not been achieved. Thus, the double stopwatch method would allow for a decrease in false positives. Meaningful pain relief is usually when 50% pain relief is achieved. Extending the time periods of the

study from sixty minutes to six hours would allow for observation of possible effects on change in mechanical allodynia over the span of a regular dosage time period.

Since a clear difference was observed between the onset of 50% pain relief between the ibuprofen sodium dihydrate and ibuprofen acid group at the low dose in this study, future studies should evaluate higher dosages (600 and 800mg) of ibuprofen sodium dihydrate in an endodontic pain model to determine the efficacy in alleviating pain relief prior to any definitive dental treatment is performed. However, precautions must be taken because all adverse events such as dyspepsia and cardiovascular problems are dose dependent.

Conclusion:

The use of ibuprofen sodium dihydrate resulted in significantly greater reduction in pain intensity, faster onset of pain relief, and greater reduction in mechanical allodynia than the use of ibuprofen acid in acute endodontic pain.

DISCUSSION

A retrospective questionnaire study concluded that individuals with symptomatic irreversible pulpitis often wait over nine days before seeking treatment as compared to patients with symptomatic necrotic teeth (28). 81-83% percent of these individuals utilized OTC analgesics and 62-65% of these patients achieved pain relief after taking the analgesics. Thus, over 35-38% of individuals in this study continued to experience pain. These patients are prone to use more than the recommended dose of an analgesic, which may result in possible dose related adverse effects. To lower the number of dose related adverse effects, we must evaluate which analgesics provide analgesia in acute odontogenic pain patients. This piece of evidence is very important in order to practice evidence-based dentistry.

We currently do not have any evidence demonstrating which analgesic will provide effective pain relief for an acute odontogenic pain patient before any definitive treatment is completed. This is the first study to evaluate this imperative area of pain control in a randomized, double-blinded clinical trial using an endodontic model. The results of this study suggest that ibuprofen sodium dihydrate had a significantly greater decrease in pain intensity, a greater attenuation in mechanical allodynia, and although marginally significant, a faster onset of 50% pain relief in comparison to ibuprofen acid.

Most patients presenting for acute endodontic pain suffer from moderate to severe spontaneous pain (4, 5, 61, 62). In this study, the intensity of spontaneous pain was measured using a validated clinical research method, a 100mm visual analog scale. Our results show that both ibuprofen acid and ibuprofen sodium dihydrate resulted in a statistically significant

decrease in intensity (50.8% and 33.3%, respectively). Ibuprofen acid has been demonstrated to be effective in odontogenic pain so the ibuprofen acid findings were as expected (28). In addition, this finding is in agreement with studies that have evaluated the two formulations using the oral surgery model (12, 72). However, ibuprofen sodium dihydrate had an 18% larger decrease of pain intensity than ibuprofen acid. These results suggest the use of ibuprofen sodium dihydrate in comparison to ibuprofen acid for spontaneous pain relief. The larger decrease in pain intensity for the sodium versus the acid formulation may be a result of a faster dissolution rate and in turn a larger bioavailability of the analgesic (10). Previous pharmacokinetic studies of ibuprofen sodium dihydrate have shown that a substantial relationship exists between ibuprofen serum levels and degree of pain relief (76). The study, which consisted of two different pharmacokinetic studies, demonstrated that the serum plasma level of ibuprofen sodium was significantly higher than that of ibuprofen acid, but it was similar to ibuprofen liquigels and ibuprofen lysinate (10). In addition, at ten minutes after administration of the two analgesics, there was a higher plasma concentration of ibuprofen sodium dihydrate as compared to ibuprofen acid.

One of the highest priorities for individuals in pain is a fast onset of pain relief (67). Three salt formulations have been introduced into the worldwide market. Ibuprofen arginate has been shown to have a faster onset of action postoperatively in patients experiencing moderate to severe odontogenic pain in comparison to ibuprofen acid (77). In addition, ibuprofen sodium dihydrate has been shown to have a faster onset of action in odontogenic pain postoperatively (12, 72). However, this study evaluated the onset of pain relief before any dental treatment has been conducted. The sodium formulation has a faster dissolution because of sodium hydrogen carbonate, an excipient of the tablet, which reacts with gastric

acid and leads to breakdown of the tablet. The resultant fine ibuprofen particles are absorbed at a faster rate than ibuprofen acid (10). The results in this study demonstrate that subjects in the ibuprofen sodium dihydrate group experienced median 50% pain relief 17.5 minutes faster than the ibuprofen acid group. The faster onset of action may translate into patients experiencing longer pain relief (69). With a faster onset of analgesia, a greater decrease in pain intensity and longer pain relief, pain patients will be less likely to take more than the recommended dose of analgesics medication. This may also result in an increase in dosage compliance rates, and a decrease in adverse events. Although the results were marginally significant, a clear differentiation was observed between the two groups.

Some common adverse effects with ibuprofen acid involve the gastrointestinal system: nausea and vomiting or the nervous system: nausea, headaches (72). Previous data from clinical trials evaluating ibuprofen acid and ibuprofen sodium in an oral surgery model have concluded that the two formulations have the same safety profile (10, 11, 72). In a clinical trial evaluating the percentage of adverse effects concluded that ibuprofen acid, ibuprofen sodium, acetaminophen, and placebo have reported adverse effects of 23.8, 30%, 30.9, and 29.6%. These adverse effects could not be related to the study treatment. Another clinical trial concluded that no serious adverse effects resulted from administration of ibuprofen acid and ibuprofen sodium (11). Based on these studies, we did not actively elicit adverse effects experienced by the cohort in this time-limited trial of a single dose analgesic. Neither did any of the subjects report any adverse effects if experienced.

It is important to note that a number of individuals in both groups did not achieve 50% pain relief within the sixty-minute trial. However, the percentages (38% of subjects in the ibuprofen acid group and 20% of subjects in the ibuprofen sodium dihydrate) of subjects

not achieving 50% pain relief within 60 minutes in this study is consistent with a previous oral surgery model study with a larger smaller size (n= 198 in each group) (12). Another study with a smaller sample size (n=80 in each group) reported a larger percentage of subjects achieving onset of 50% pain relief within 60 minutes (72). There are a couple of reasons why this could occur. Firstly, a low dose (400mg of ibuprofen acid and an equivalent dose of 512 mg of ibuprofen sodium dihydrate) of analgesic was administered to patients in this study. According to the Oxford League Table of Analgesic Efficacy, 400mg of ibuprofen results in 55% of pain relief over a span of 4-6 hours, while 600-800mg of ibuprofen acid results in 86% pain relief over a span of 4-6 hours (77). Secondly, the study concluded at sixty minutes and this may not have been enough time for the analgesic serum levels to reach proper analgesic levels. Thirdly, as seen in this and other studies, a subset of individuals may not respond to ibuprofen (12). This group of patients may require a supplemental type of analgesic, such as acetaminophen, to obtain effective pain relief.

This is the first study to report differences in mechanical pain thresholds after administration of ibuprofen sodium dihydrate. In this study, the contralateral tooth was used as the control for mechanical allodynia calculations. All control teeth were tested clinically and the teeth did not display an exacerbated or lingering response to thermal stimuli and did not have sensitivity to percussion. Only a clinical exam was conducted on the control teeth and the pulpal diagnosis was normal pulp and periapical diagnosis was normal apical tissues. Previous studies have concluded that under normal conditions any pair of contralateral teeth has the same mechanical pain threshold levels (42). Thus, the tooth type did not affect the total mechanical allodynia data. Although the change in mechanical allodynia in the ibuprofen sodium dihydrate group was 15%, it was statistically significant. This change was

not observed in the ibuprofen acid group. Clinically, a 15% change in mechanical allodynia may translate into the difference between the patient being unable to touch the tooth without severe pain preoperatively to being able to tolerate light touch and possible mastication of soft foods after sixty minutes of administration. These results are different from the ones reported in a previous study that evaluated the mechanical pain thresholds of patients with periapical diagnosis of symptomatic apical periodontitis but patients had various pulpal diagnosis: previously initiated treatment, pulp necrosis, and symptomatic irreversible pulpitis teeth with the pre-administration and post-administration of 800mg of ibuprofen acid. The results from the study indicated that mechanical pain thresholds did not increase in affected teeth but increased 20-28% in control teeth (45).

Mechanical allodynia is a decrease in mechanical pain threshold and results from peripheral and central sensitization (41). Since this study was concluded at sixty minutes, there is a possibility that not enough time had lapsed for the analgesic to affect the central sensitization component of mechanical allodynia. A larger difference in mechanical allodynia may have been found if the study was extended to more than one hour. The study was concluded at sixty minutes because individuals enrolled in the study presented to the dental school in acute odontogenic pain. We felt that it would not be ethical to keep the non-responders in for longer than a normal diagnostic period.

We observed differences with regards to the gender of the patient. In this study, females often presented with a higher intensity in pain when compared to males. This trend has been observed in previous studies evaluating odontogenic pain (16, 28, 41). Females also reported a higher level of pain relief than their male counterparts. No significant differences were found between the two medications. This study was not designed to look for these

differences and it did not have enough power to confidently report these differences. These gender differences need further evaluation for possibly significant correlations.

Most studies on the use of analgesics in the endodontic literature focus on its effect on postoperative pain or as an adjunct to obtaining profound local anesthesia (64, 65, 78-80). Based on these studies, the current recommendation for pain relief include the use of 600mg ibuprofen or a combination of 650mg ibuprofen with 1000 mg of acetaminophen for pain relief (64, 65). It is important to note that the dose used in this study for both ibuprofen formulations is significantly lower than the current recommended dose. It can be inferred that the current recommended dose of ibuprofen acid (600mg) if translated to ibuprofen sodium dihydrate (768 mg) could potentially have a larger decrease in pain intensity, a larger change in mechanical allodynia and possibly a faster onset of action. Further research studies are needed to confirm this assumption. The results from this study suggest that the oral surgery model and the endodontic model have similar results when evaluating the decrease of pain intensity and the onset of 50% of pain relief.

The use of a placebo in clinical trials is of great debate. In clinical pain trials, there is an ethical conflict about providing individuals with a placebo, an inert substance, when an effective pain management therapy is already present. The placebo effect has already been reported for inflammatory agents in randomized, double blind, and placebo-controlled analgesic clinical trials on The Oxford League Table of Analgesic Efficacy (74). Studies have additionally concluded that the placebo effect can be present even without the presence of a placebo (81). Thus, a placebo was intentionally not incorporated into this research design because previous studies have shown that ibuprofen is effective at alleviating odontogenic pain.

There are inherent challenges within the endodontic pain model that make it difficult to recruit subjects for the study. One such challenge is that subjects are often in moderate to severe pain and tend to pre-medicate themselves prior to their dental appointments. In this study, the strict inclusion and exclusion criteria, as well as, the inability to contact many individuals prior to their dental appointments resulted in a small sample size for this study. In addition, a future study may benefit from using a double stopwatch method in which an individual is asked to stop one stopwatch at the first sign of pain relief and stop a second stopwatch when meaningful pain relief is achieved. Meaningful pain relief is usually when 50% pain relief is achieved. Furthermore, extending the time periods of the study from sixty minutes to six hours would allow for observation of possible effects on change in mechanical allodynia over the span of a regular dosage time period. Since a clear difference was observed between the onset of 50% pain relief between the ibuprofen sodium dihydrate and ibuprofen acid group at the low dose in this study, future studies should evaluate higher dosages (600 and 800mg) of ibuprofen sodium dihydrate to determine the efficacy in alleviating pain relief prior to any definitive dental treatment is performed.

The results in this study are very applicable in daily clinical practice. Firstly, ibuprofen sodium dihydrate would be a useful adjunct if a patient is unable to be seen by a dentist due to time or finances. Instead of the patient having continuous pain or having to visit at the ED, the patient can utilize this OTC formulation for predictable pain relief until definitive dental treatment can be rendered. In addition, the new ibuprofen formulation may help in obtaining successful local anesthesia as shown in a previous study with ibuprofen acid (78). In addition, pre-emptive administration of ibuprofen can have an effect on post-operative pain (82). Patients presenting to the clinic with acute odontogenic pain have an

ongoing inflammatory process from a polymicrobial insult. The trauma from the emergency dental treatment will result in further exacerbation of this inflammatory process. Pre-emptive administration of ibuprofen may decrease the formation of new inflammatory mediators due to the trauma or at least reduce the total inflammatory mediator load in the area.

Conclusion:

The use ibuprofen sodium dihydrate preoperatively provides a larger decrease in pain intensity, a larger change in mechanical allodynia, and although marginally significant, a faster onset of 50% pain relief in comparison to ibuprofen acid in an endodontic pain model.

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